REMARKS

Applicant has amended claims 1 and 31 and canceled claims 2, 4, 11, 21, and 34-40 herewith. The cancellation of these claims by the Applicant to advance prosecution of the remaining claims should not be construed as any admission by the Applicant that the Office's allegations of unpatentability of these claims are correct. Furthermore, the Applicant expressly reserves their right to pursue such subject matter in related continuation and/or divisional patent applications.

ELECTION/RESTRICTIONS

Applicant has canceled herewith claims that were previously withdrawn for the purpose of advancing prosecution of the remaining claims. The cancellation of such claims and the absence of counterarguments in this Response to the reasons for making the Restriction final advanced by the Office should not be construed as any admission by the Applicant that the Restriction is proper or warranted.

REJECTIONS OF CLAIMS UNDER 35 USC §112, 1st PARAGRAPH: WRITTEN DESCRIPTION

In the Office Action, previously pending claims 1-2, 9-10, 21, 26, and 31-32 were rejected under 35 USC §112, 1st paragraph, as allegedly failing to meet the written description requirement. The Office alleged that: i) the specification failed to demonstrate that the Applicant was in possession of the claimed genus of LPS O-antigens; ii) that the claims are drawn to a "vast genus of LPS O-antigen side chains", iii) that the specification does not provided a correlation between the structure and function of LPS O-antigens; and iv) that the "**Applicant has not demonstrated any LPS O-antigen capable of being conserved among all Salmonella species and E.coli strains and capable of enhancing the ability to induce cross protective immunity against *Salmonella species and E.coli* strains in an attenuated strain**" (as emphasized by the Office on Page 7 of the Office Action).

With respect to items i, ii, and iv, the Applicant respectfully notes that the claims as currently amended are drawn to a live attenuated strain of Salmonella comprising "a means for

regulating synthesis of an LPS O-antigen, wherein said LPS O-antigen ceases to be synthesized in vivo, exposing an LPS core oligosaccharide antigen that is conserved among *Salmonella* species" (emphasis added). The claims are not drawn to a genus of LPS O-antigens, but rather to live attenuated strains of *Salmonella* that regulate synthesis of such LPS O-antigens. Furthermore, the claims indicate that it is the LPS core oligosaccharide antigen rather than the LPS O-antigen that is conserved. The specification clearly outlines that "(t)he core region of LPS is highly conserved, in contrast to the O-antigen which is the basis for distinguishing the various serotypes of many Enterobacteriaceae species" (see first full paragraph page 18 of the specification as originally filed). The specification further indicates that "LPS O-antigens are antigenically diverse as between strains of Enterobacteriaceae, and are a major factor in the variable immune response of host organisms to different strains of bacteria" (see second full paragraph on page 18 of the specification as originally filed). The variability of LPS O-antigens is also described in by the Reeves et al. reference that was cited in the specification (see Reeves, P. 1995. Role of O-Antigen Variation in the Immune Response. Trends Microbiol. 3:381-386 provided previously in IDS of October 1, 2007). It is thus not at all clear that the Applicant should be required to demonstrate "**any LPS O-antigen capable of being conserved among all Salmonella species and E.coli strains"** when the specification in fact indicates that such LPS O-antigens are not conserved and when the claims are not drawn in any way to "conserved" LPS-O antigens.

As noted previously, the Application as filed does disclose various means for regulating synthesis of LPS-O antigens as claimed. More specifically, the specification discloses both mutations in or regulation of genes of the *rfb* gene cluster as well as mutations in the *pmi* gene that are suitable for regulating expression of LPS O-antigens (on pages 12, 18-20). On page 20, the specification further indicates that such regulation can be achieved by replacing a promoter for any of the *rfb* genes that are needed for synthesis of the LPS O-antigen with the *araC*P_{BAD} activator-repressor-promoter system. One of ordinary skill in the art would thus clearly understand that the Applicant was in possession of various means for regulating synthesis of LPS O-antigens as currently claimed.

In considering compliance with the written description requirement, we also note that the courts have clearly held that one must consider the state of the art at the time of filing and that

well known biomolecules need not be defined by sequences or structures. As noted in the MPEP:

> What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. See Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d at 1384, 231 USPQ at 94. >See also Capon v. Eshhar, 418 F.3d 1349, 1357, 76 USPQ2d 1078, 1085 (Fed. Cir. 2005)("The 'written description' requirement must be applied in the context of the particular invention and the state of the knowledge.. As each field evolves, the balance also evolves between what is known and what is added by each inventive contribution."). (MPEP§2163.II.3).
>
> Although structural formulas provide a convenient method of demonstrating possession of specific molecules, other identifying characteristics or combinations of characteristics may demonstrate the requisite possession. >As explained by the Federal Circuit, "(1) examples are not necessary to support the adequacy of a written description; (2) the written description standard may be met even where actual reduction to practice of an invention is absent; and (3) there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure." Falkner v. Inglis, 448 F.3d 1357, 1366, 79 USPQ2d 1001, 1007 (Fed. Cir. 2006). See also Capon v. Eshhar, 418 F.3d at 1358, 76 USPQ2d at 1084 ("The Board erred in holding that the specifications do not meet the written description requirement because they do not reiterate the structure or formula or chemical name for the nucleotide sequences of the claimed chimeric genes" where the genes were novel combinations of known DNA segments.). (MPEP§2163.II.3).

This position has recently been affirmed in a recent en banc decision by the Federal Circuit Court in *Ariad v. Eli Lilly*, 598 F. 3d 1336, 2010:

> For generic claims, we have set forth a number of factors for evaluating the adequacy of the disclosure, including "the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or

technology, [and] the predictability of the aspect at issue". (in *Ariad v. Eli Lilly*, *Ibid.* at 1351, citing *Capon v. Eshhar*, 418 F.3d 1349)

In this case, the state of the art with respect to LPS O-antigens and their regulation was well developed and extensive at the time of filing. The specification in fact provides a variety of references that describe both the structures and functions of LPS O-antigens and their regulation (see references 23-29, 40, 41, 43, 44, and 49 on pages 6-8). Given that LPS O-antigens and their regulation, like the immune-related DNA components of *Capon v. Eshhar*, were well known at the time of filing, the specification need not provide an extensive set of LPS O-antigen sequences or correlation between the structure and function of LPS O-antigens to meet the written description requirement. At the time of filing, methods for regulating LPS O-antigen synthesis as claimed were extensively described in both the specification and literature referenced therein. Regulation of LPS O-antigen synthesis could be predictably achieved by mutations in or regulation of genes of the *rfb* gene cluster as well as mutations in the *pmi* gene as described in the specification and literature cited therein. Furthermore, the state of the art with respect to conservation of the LPS core oligosaccharide across *Salmonella* and *E. coli* strains was also well developed at the time of filing (see Heinrichs et al., Molecular Microbiology (1998) 30(2), 221–232 and Di Padova et al. (1993) Infect. Immun. 61(9):3863, both in the accompanying IDS). As such, one of skill in the art would have recognized that the Applicant was in fact in possession of the invention as claimed.

In view of these considerations and those provided in previous Responses, Applicant respectfully requests that the Examiner withdraw the rejections of the claims under 35 USC §112, first paragraph, for lack of written description.

REJECTIONS OF CLAIMS UNDER 35 USC §112, 1st PARAGRAPH: ENABLEMENT

In the Office Action, previously pending claims 1-2, 9-10, 21, 26, and 31-32 were rejected under 35 USC §112, 1st paragraph, as allegedly failing to meet the enablement requirement.

Considering the relevant *Wands* factor of claim breadth, Applicant first notes that the claims as currently amended are drawn to a live attenuated strain of *Salmonella* wherein an LPS core oligosaccharide antigen that is conserved among *Salmonella* species is exposed and wherein the attenuated strain has enhanced ability to induce cross-protective immunity against *Salmonella* species (see claim 1 and other pending claims that depend therefrom as currently amended). As such, any of the Office's rejections based on an alleged lack of enablement of previously pending claim elements such as "*E. coli*" are rendered moot. Similarly, any of the Office's rejections based on an alleged lack of enablement of previously pending claim elements such as "vaccine" are also rendered moot. The question at hand is whether one of ordinary skill in the art could make and use a live attenuated strain of *Salmonella* as currently claimed without undue experimentation.

In rejecting the claims for lack of enablement, the Office suggests that the specification only enables one exemplary strain disclosed in the examples (i.e. Δpmi-2426 ΔPfur223;;TT *araC* P_{BAD}). However, the Office is respectfully reminded that enablement does not turn on the numbers of examples provided and that all relevant *Wands* factors must be considered. The MPEP states:

> For a claimed genus, *representative examples* together with a *statement applicable to the genus as a whole* will ordinarily be sufficient if one skilled in the art (in view of *level of skill*, *state of the art* and the *information in the specification)* would expect the claimed genus could be used in that manner without undue experimentation. Proof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation. (MPEP§2164.02, *emphasis added*)

An examination of this case indicates that such *representative examples*, *statements* applicable to the genus as a whole, the *level of skill*, the *state of the art* and *information in the specification* indicate that live attenuated strains of *Salmonella* claimed herewith could be made and used without undue experimentation. First, *representative working examples* where a live attenuated *Salmonella* strains provided an increase in survivorship following a challenge by virulent wild-type *Salmonella* strains of two distinct groups are provided in Example 6 (χ3761: Group B *S.*

typhimurium UK-1) and Example 7 (χ3761: Group D *S. enteridis*). Second, *statements applicable to the genus* of live attenuated *Salmonella* strains are found in at least the first paragraph of the Summary of Invention (page 11 of the specification), Example 1 (which provides a table of various *Salmonella* that includes groups B, C, D, and E), and Example 13 (which describes how to construct live attenuated strains of host-specific Salmonella serotypes of *S. choleraesuis*, *S. dublin*, *S. paratyphi*, and *S. typhi* using the same vectors and methods used to construct the exemplary strain). Third, *the level of skill* in the field of live attenuated *Salmonella* strains would typically comprise an individual with a doctoral degree who is versed in molecular and bacterial genetics. Fourth, such an individual would have the advantage of operating at a point in time where the *state of the art* with respect to the field of live attenuated *Salmonella* strains, the *araC*P_{BAD} activator-repressor-promoter system, *fur* genes, and regulation of LPS O-antigen genes was exceptionally well developed. The *state of the art* was clearly advanced at the time of filing with respect to the *araC*P_{BAD} activator-repressor-promoter system (Guzman et al., J.Bacteriol. 177:4121, 1995, cited on page 9 of the specification and provided previously in the IDS of October 1, 2007), *Salmonella fur* genes (Hall and Foster, J.Bacteriol. 178:5683, 1996, cited on page 8 of the specification and provided previously in the IDS of October 1, 2007), and regulation of LPS O-antigen synthesis (Collins et al., Infect. Immun. 59:1079, 1991, cited on page 7 of the specification and provided previously in the IDS of October 1, 2007). Finally, the specification itself provides significant guidance with respect to both *araC*P_{BAD} activator-repressor-promoter system control of *fur* (see paragraph spanning page 21 and 22 of the specification as well as pages 29-30) and regulation of LPS O-antigen synthesis (see pages 12, 18-20 of the specification). These factors thus suggest that one skilled in art could, in light of the guidance provided by the specification, obtain any of the distinct *Salmonella* strains described in literature cited in the specification or elsewhere, place the *fur* gene of that strain under the control of an *araC*P_{BAD} activator-repressor-promoter system, and regulate synthesis of the LPS O-antigen genes through nothing more than routine experimentation.

The Office also appears to require that the Applicant demonstrate "a protective response in a host, for prevention of *Salmonella* and *E.coli* as is a requisite of a vaccine" (Page 18 of the Office Action) and states that "the exhibit of 80-100% survivorship does not indicates prevention (i.e. vaccine)" (Page 12 of the Office Action). An exhibition of 80-100% survivorship upon

challenge by virulent *Salmonella* relative to unprotected controls that exhibit 0% survivorship as shown in Examples 6 and 7 of the specification as filed certainly is evidence of a "protective response" and certainly satisfies what is specified in the claims ("attenuated strain has enhanced ability to induce cross-protective immunity against *Salmonella* specie"). Should the Office maintain enablement rejections of the currently pending claims for failure to exhibit "prevention of *Salmonella*", Applicant would respectfully request the Office provide an explanation as to what "prevention of *Salmonella*" might comprise, why working examples of 80-100% survivorship does not constitute an enhanced ability to induce cross-protective immunity against *Salmonella* specie as currently claimed, and what basis there is in the law for requiring that the claims enable a performance standard specified by the Office rather than the claims.

Applicants further maintain as per their previous Response that (t)he working examples do in fact provide empirical data or results indicative of a preventing *Salmonella* and *E.coli* infection as claimed, that the models provided in the specification are in fact art accepted as evidenced by their acceptance in peer reviewed scientific journals, that the Bolin et al. and Sood et al. references provided by the Office indicate that IROMPs apparently fall in that subset of antigens that do result in a certain level of a protective response to infection and thus support enablement, and that the Greenspan et al. reference is irrelevant to enablement of the invention as currently claimed.

In view of these considerations and those provided in previous Responses, the Applicant respectfully requests that the Examiner withdraw the rejections of the claims under 35 USC §112, first paragraph, for lack of enablement.

CONCLUSION

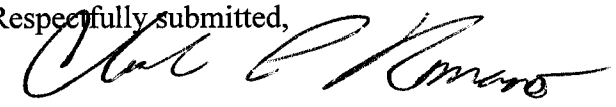
Applicant believes that a complete response to the Office Action of June 23, 2010 is provided herewith and respectfully request that the Office reconsider and withdraw the rejections of the claims in light of the amendments and remarks provided herein.

It is not believed that extensions of time are required beyond those which may otherwise be provided for in this filing. In the event however that additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby

petitioned for under 37 C.F.R. §1.136(a), and any fees required therefore are hereby authorized to be charged to our Deposit Account 20-0823.

The Examiner is encouraged to contact the undersigned via telephone at the number provided, if it is determined that personal communication will expedite prosecution of this application.

Respectfully submitted,



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